

*Clinico-pathological conference***Adult respiratory distress syndrome complicating *Pneumocystis carinii* pneumonia**

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Case report (Dr A Scoular)

This 34 year old man presented with a 3 week history of fever, dry cough and exertional dyspnoea. He had returned from holiday in Madeira only 2 days previously. He was a non-smoker and drank alcohol moderately. In the past he had been treated for syphilis in 1974. At that time he also had genital herpes. He remained well until 1980 when he presented with acute hepatitis A and was also found to be hepatitis B immune, with positive anti-core and anti-surface antibodies. In September 1988 he presented with cutaneous lesions of Kaposi's sarcoma and was found to be HIV-1 antibody positive. He commenced zidovudine shortly afterwards. He was looked after at another hospital and remained well for approximately 1 year when he developed oesophageal candida, increasingly widespread lesions of Kaposi's sarcoma and was commenced on α -interferon therapy. Despite this his Kaposi's sarcoma skin lesions continued to enlarge and become more widespread. At this point his CD4 count was 30 and he was p24 antigen positive. Therapy was then changed and epirubicin was given on a weekly basis but he became anaemic very quickly on this and so it was temporarily discontinued. Shortly afterwards he was admitted to this hospital. At the time of admission he was taking zidovudine 250 mg tds, acyclovir 400 mg tds, and Fansidar (pyrimethamine 25 mg and sulfadoxine 500 mg) 1 tablet per week (as primary prophylaxis against *Pneumocystis carinii* pneumonia as he was thought to be allergic to co-trimoxazole) and epirubicin 20 mg once a week. On examination at the time of admission he was febrile at 37.8°C, he had widespread lesions of cutaneous and also oral

Kaposi's sarcoma. His heart rate was 84 per minute, his blood pressure was 110/70 mm Hg and he had a respiratory rate of 18 per minute. Auscultation of the chest revealed no significant abnormalities and the rest of the examination was normal. On admission a chest radiograph was performed (fig 1). This showed bilateral interstitial shadowing in the upper zones, the mid and lower zones were relatively clear. Investigations showed he was anaemic with a haemoglobin of 8.9 g/dl; the white cell count was $1.8 \times 10^9/l$ with 50% neutrophils. Arterial blood gases taken breathing air showed a PO_2 of 12.1 kPa and a PCO_2 of 3.9 kPa. Blood cultures, urea and electrolytes, and liver function tests showed no abnormalities. Serologically he had evidence of previously treated syphilis and immunity to hepatitis B. A provisional diagnosis of *Pneumocystis carinii* pneumonia was made and bronchoscopy was planned for the following day; treatment was begun with nebulised pentamidine and the zidovudine was discontinued. At bronchoscopy the bronchial tree was normal and no endobronchial Kaposi's sarcoma was seen. Laboratory examination of the broncho-alveolar lavage fluid showed only *Pneumocystis carinii*; subsequent culture was sterile. After 5 days of nebulised pentamidine the patient was still spiking a fever although he felt better. He was active, mobile and self-caring around the ward. At this point repeat blood cultures were performed which were negative; he remained pyrexial. On day 6 of the admission he was transfused with 4 units of blood. One week after admission the patient was slightly more breathless but otherwise remained clinically well, his arterial blood gases had shown a marked deterioration, his PO_2 breathing air having fallen to 6.1 kPa, and PCO_2 remaining at 3.9 kPa. A repeat chest radiograph on day 9 showed more extensive alveolar shadowing (fig 2). As the patient had continuing fever it was considered that a change in therapy was appropriate. Intravenous pentamidine was begun and a 3-day course of mega-dose methylprednisolone (1 g per day intravenously) was given. The following day the patient had improved and blood gases showed a PO_2 of 10.3 kPa on air. By day 11 the patient was very much improved, he was afebrile for the first time and symptomatically felt better. Four days later (on

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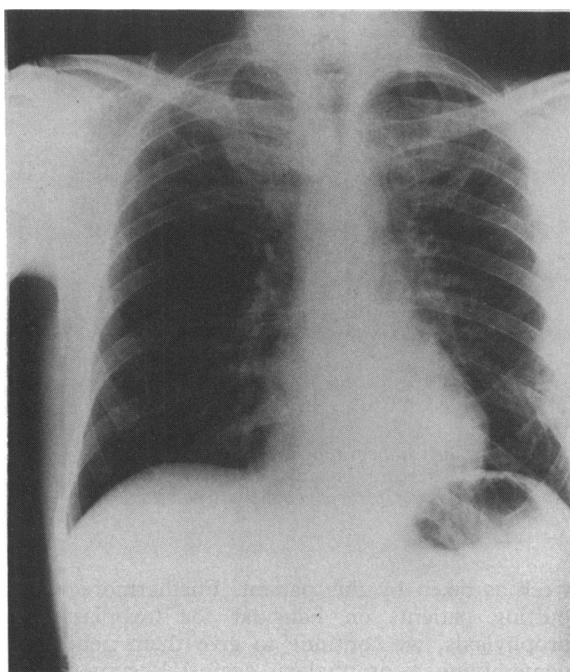


Figure 1 Chest radiograph on admission showing bilateral upper zone shadowing, the mid and lower zones are relatively clear.

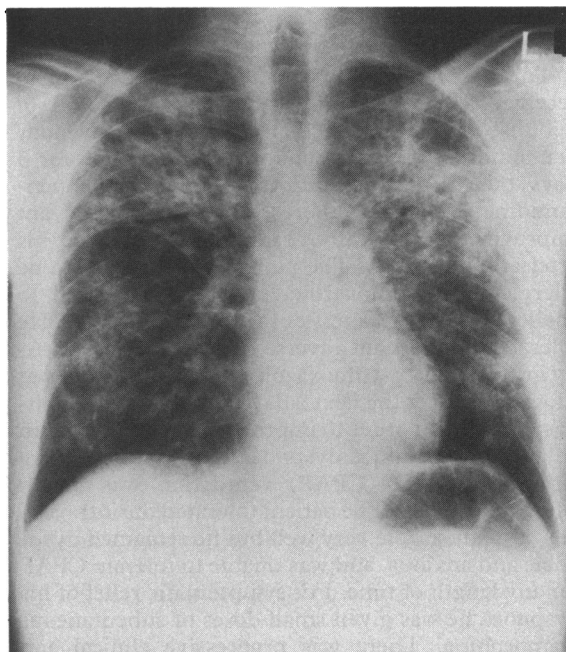


Figure 3 Chest radiograph, day 16, showing there has been no improvement.

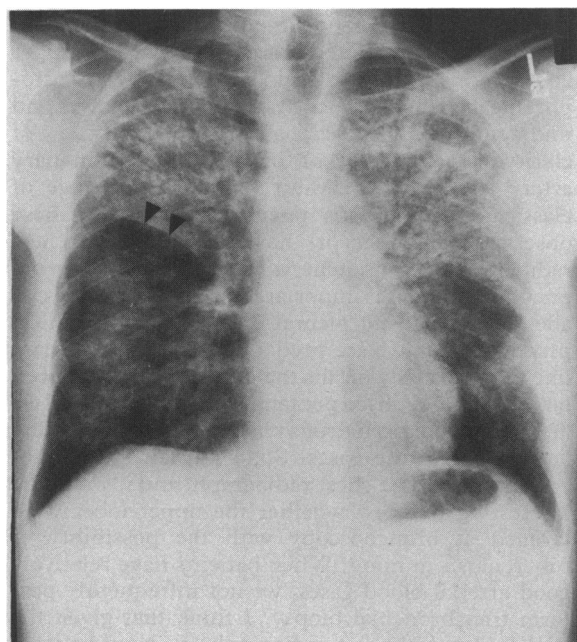


Figure 2 Chest radiograph, day 9, showing more extensive shadowing in the upper zones. There is also mid and lower zone shadowing, with sparing of the costophrenic angles. There is volume loss in the right upper lobe and the lesser fissure is pulled up (arrows).

the eighth day of intravenous pentamidine) the patient remained afebrile, and was again mobile and self-caring. Arterial blood gases showed a PO_2 of 9.3 kPa on air. The serum albumin had fallen to 23 g/l as had his sodium level. The chest radiograph on the 16th day of the admission showed no significant improvement (fig 3), but the patient had improved clinically. The only event of note at this stage was thrombocytopenia (platelet count = $22 \times 10^6/l$). There was no spontaneous bleeding nor easy bruising.

It was felt that the patient had improved sufficiently to consider changing back to nebulised pentamidine therapy; however, within 48 hours he again became dyspnoeic, intravenous pentamidine was recommenced and nebulised therapy was stopped. The slight clinical deterioration was paralleled by his arterial blood gases, the PO_2 had fallen to 8.4 kPa on air. On the 21st day of his admission the patient was still pyrexial. A bacterial co-infection was thought possible and so intravenous cefuroxime 750 mg tds was added empirically. Blood and urine cultures prior to starting cefuroxime were negative; the patient was unable to spontaneously expectorate sputum. Over the next 2 days there was further deterioration in blood gases so a repeat bronchoscopy was carried out on day 24. The endobronchial appearances were again normal. *Pneumocystis carinii* was again seen in the lavage together with a heavy growth of *Enterobacter cloacae* which was fully sensitive to cefuroxime. A chest radiograph (fig 4) taken

on day 26 showed a marked deterioration. The PO_2 breathing 60% oxygen was 7.5 kPa.

To summarise events up to day 27, the patient had received 4 weeks therapy, comprising 8 days of nebulised pentamidine, then 9 days of intravenous pentamidine, back on nebulised pentamidine for 3 days then a further 8 days of intravenous pentamidine. Overall there was no significant improvement clinically, radiologically or in his arterial blood gases. The patient was thought to be allergic to co-trimoxazole, but it was decided to challenge him with a test dose of co-trimoxazole. He tolerated this without adverse effects and subsequently intravenous co-trimoxazole was begun, initially at a low-dose, over the next 2 days increasing to a high-dose regime. In order to improve oxygenation and in an attempt to reduce dyspnoea continuous positive airways pressure (CPAP) ventilation was begun using a face mask. The patient tolerated the intravenous co-trimoxazole very well but he remained dyspnoeic and anxious, and was unable to tolerate CPAP for any length of time. For symptomatic relief of his dyspnoea he was given small doses of subcutaneous diamorphine. There was progressive clinical and radiographical deterioration and on day 31 the patient was given a further 3-day course of intravenous methylprednisolone, which did not produce any improvement. The patient became progressively more distressed and tired, and was given increasing doses of diamorphine to relieve his dyspnoea. Subsequently he expressed a wish to discontinue all active treatment and died peacefully.

Discussion (Professor J Moxham)

This patient was at high risk of *Pneumocystis carinii* pneumonia. At the time of his current admission the CD4 count was less than 30 and he was antigen positive. Such an extremely immunosuppressed patient is almost certain to develop *Pneumocystis carinii* pneumonia sooner or later.¹ This being the case, most centres now use prophylaxis against pneumocystis and commonly this is with nebulised pentamidine in doses of 300 mg or more each month.² This prophylaxis is extremely effective. Probably the only patients who subsequently develop pneumocystis pneumonia with the occasional exception are patients who do not take their prophylaxis correctly. An alternative regime for prophylaxis would be oral co-trimoxazole. My own preference is for nebulised pentamidine because I am always concerned that patients may develop sulphonamide sensitivity. A further alternative would be dapsone 100 mg daily. We do not use Fansidar as prophylaxis, and I am not aware of any large studies that have evaluated it as prophylaxis for *Pneumocystis carinii* pneumonia. We use Fansidar as prophylaxis against toxoplasmosis but at a dose of one tablet twice a week, and not once a

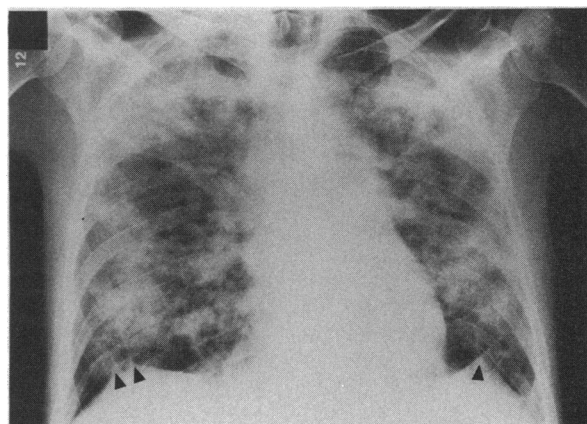


Figure 4 Chest radiograph, day 26. The appearances have deteriorated markedly. In addition to extensive patchy alveolar shadowing, pleural changes are now evident (arrows).

week as taken by this patient. Furthermore when putting patients on Fansidar for toxoplasmosis prophylaxis, we continue to give them nebulised pentamidine as prophylaxis against *Pneumocystis*. Overall I am not surprised that this patient developed *Pneumocystis carinii* pneumonia.

Turning to the patient's presentation with pneumocystis pneumonia, the chest radiograph is rather unusual (fig 1). It is characteristic of *Pneumocystis carinii* pneumonia that the mid and lower zones are affected more often than the upper zones. We are used to seeing sparing of the costophrenic angles, but we are not used to the lower and mid zones being as clear as in this patient. Lack of clarity of the branches of the right basal pulmonary artery is often the earliest radiological change of classical pneumocystis pneumonia. Despite these observations, I accept, however, that the chest radiograph is consistent with *Pneumocystis carinii* pneumonia and it is important to note that there is no adenopathy and no pleural disease. In our clinical practice, when we see predominantly apical disease like this, it usually means that patients have not been taking their nebulised pentamidine effectively and we know that nebulised drugs reach the apex of the lung less well than the bases. So, I am left with slight concern about the chest radiograph, and it would be interesting to know whether the upper lobes were lavaged at bronchoscopy with the possibility of tuberculosis in mind. When patients have relatively good arterial blood gases, we not infrequently perform transbronchial biopsy. I think that given the slightly atypical chest radiograph, we would almost certainly have biopsied this patient. Sometimes such transbronchial biopsies provide additional, useful information.

Let us, for the moment, assume that the diagnosis

of *Pneumocystis carinii* pneumonia is secure. Assessing the severity of the illness is crucially important. We are given the information that the patient had symptoms for 3 weeks, which is about average for *Pneumocystis carinii* pneumonia. I had been informed that the patient was breathless on dressing, and breathlessness in patients who are performing such minor tasks is a good indication that the respiratory system is under considerable stress. On that basis I would have graded the pneumonia as moderately severe. The chest radiograph changes are obvious and affect both lungs, and once again I would grade them as being of moderate severity. The arterial hypoxaemia is relatively mild but there is widening of the alveolar-arterial oxygen gradient. Taking into account the history, examination and chest radiograph, my conclusion would be that this patient had a moderate disease. In view of the treatment that this patient subsequently received, this initial assessment is crucial.

In most circumstances the treatment of choice for *Pneumocystis carinii* pneumonia is high-dose intravenous co-trimoxazole.³ I know of no literature to suggest that any other treatment is superior, and there are some data to suggest that some treatments are not as good. In this particular case there was a possible problem of the patient being allergic to co-trimoxazole. Usually this allergy is due to the sulphonamide component of the drug and it is surprising that the patient was taking regular Fansidar. Fansidar has been noted to cause rather more allergy problems than co-trimoxazole. The sulphonamide in Fansidar has a longer half life and the drug has produced a Stevens-Johnson syndrome in a number of patients. On the available evidence, I would not have accepted that this patient was allergic to sulphonamides and would have treated him with intravenous high-dose co-trimoxazole, keeping a careful eye on his response. If the patient were truly allergic, then our first strategy would be to treat him with trimethoprim and dapsone, a regime that is found very effective in these circumstances.⁴

The decision was made by the clinicians caring for the patient, to give this patient nebulised pentamidine. Much of what we know about nebulised pentamidine as therapy for pneumocystis pneumonia comes from this hospital. As I understand the data, nebulised pentamidine is best reserved for patients with mild to moderate disease, and in such patients an 80% response rate is to be expected.⁵ Furthermore, the clinical response will be slower than when co-trimoxazole is used. Looked at from a different viewpoint, we can say that in 20% of patients with mild to moderate disease nebulised pentamidine will fail and it might be a week or so before it is clear that the therapy is failing. Most physicians would not treat patients with *Pneumocystis carinii* pneumonia with nebulised pentamidine, except when confident that the disease is mild.

On admission the patient was anaemic and he was taking zidovudine 250 mg tds; this drug was stopped. It is our usual practice to stop zidovudine when we are treating patients with pneumocystis pneumonia because both the disease itself and therapy depress marrow function, which can cause substantial difficulties in the delivery of adequate treatment for the pneumonia.

Reviewing the results of the first week of therapy with nebulised pentamidine, we are told that the arterial tension started at 12.1 kPa and ended at 6.1 kPa. Clearly the patient had deteriorated and was in the 20% or so of patients who do not respond well to nebulised therapy. The questions that then arose were firstly whether the patient's treatment should be altered and if so which drug should be used, and secondly whether there was a place for steroid therapy. We use steroids frequently in our patients, and we use them early. I suspect that a fall in PaO₂ from 12 to 10 kPa would have been sufficient indication for us to have used steroids and to have changed the patient's therapy. As I have indicated we prefer co-trimoxazole for the treatment of pneumocystis pneumonia and would have changed the patient to this drug, or if we had been persuaded about allergy to sulphonamide, we would have used trimethoprim and dapsone.

After 1 week of therapy the patient's treatment was changed to intravenous pentamidine, and he was also given methylprednisolone. It is possible to predict with a fair degree of accuracy what would then happen. As soon as patients are given steroids they improve rapidly.^{6,7} *Pneumocystis carinii* pneumonia causes very leaky lung vasculature and steroids improve this situation, and blood gases rapidly get better. The hope is that this improvement buys time for the drug therapy to get on top of the infection. In this patient the PO₂ dramatically improved within 24 hours of starting steroids. I would stress that this had nothing to do with the treatment of the underlying pneumocystis pneumonia. We know that intravenous pentamidine is slow to have much effect because the accumulation of the drug in the lung takes several days, and only has maximum effect approximately 1 week after starting therapy.^{3,8} This patient was given mega-dose steroids for 3 days, other centres may use lower doses for longer periods.⁷ Most of our patients who get steroids are treated for 7–10 days, after which we gradually tail off the dose. I would not normally think of reducing the dose of steroids unless I was absolutely certain that the specific anti-pneumocystis therapy was being effective.

By the end of the second week of treatment, at which time the patient was continuing to receive IV pentamidine, there appeared to be some gradual improvement. Partly because of the low platelet count and also because it was thought that the patient was sufficiently improved, he was switched from intravenous to nebulised pentamidine. We have

already observed that the patient did not respond well to nebulised pentamidine when his disease was judged to be no less severe, and it seems unlikely, certainly in retrospect, that nebulised pentamidine would be any more effective at this later stage.

The patient deteriorated and the question was raised as to whether there was a second pathogen. This is, of course, a common clinical dilemma in such patients, and particularly in cases such as this when, after three weeks of therapy, the patient is rather worse than on admission. The chest radiographs were showing deterioration and, particular in view of the upper lobe disease, I would certainly have also been concerned about the possibility of tuberculosis. At rebronchoscopy *Pneumocystis carinii* was again found, together with *Enterobacter cloacae*. I noted that the bronchial tree looked normal. One of the extraordinary things about pneumocystis pneumonia is that even in a patient dying of hypoxaemia the bronchial tree looks entirely normal. In some patients who have a complicating bronchial infection, as sometimes occurs in those with a low neutrophil count, the bronchial mucosa may be markedly inflamed. At this stage, the patient returned to intravenous pentamidine but there was the challenge of having to make up for the few days when intravenous therapy had been discontinued. By the 4th week of treatment the patient was desperately ill. The PO_2 was 9.3 kPa, but this was on 60% oxygen and lungs were clearly in advanced failure. By now the patient had very severe *Pneumocystis carinii* pneumonia, and I would also have predicted that he had advanced adult respiratory distress syndrome (ARDS). In an attempt to improve oxygenation CPAP was tried.⁹ Although this produced improved blood gases, the patient was unable to tolerate the treatment so you had to discontinue it.

If lung biopsies are undertaken in patients with advanced pneumocystis pneumonia who are deteriorating after 2 or 3 weeks treatment, what is seen by the pathologist is ARDS and a great deal of hyaline membrane formation. The lung is virtually solid and there are many fibroblasts and some organised fibrous tissue and only scant evidence of *P. carinii* organisms present.¹⁰ It would appear that the treatment often cures the infection but the patient died because of the ARDS initiated in the lung. In this patient I think the situation might be slightly different, because repeated lavage late in the illness showed persistent *P. carinii* and I do not think that the treatment ever really coped with the infection. I would predict that the pathology will show organising pneumocystis pneumonia as well as advanced ARDS.

Dr R Miller

You say you perform transbronchial biopsies in some patients and that these sometimes provide additional

information. This has not been our experience.¹¹ Are you concerned by the increased rate of complications reported in HIV-1 positive patients undergoing transbronchial biopsies? In whom should transbronchial biopsies be performed? Is there a cost-benefit ratio?

Professor J Moxham

I accept that there is an increased risk of performing transbronchial biopsies in HIV positive patients, although I am not sure how clinically important this is. Certainly we have never caused a patient great harm. We certainly do not perform transbronchial biopsies in most of patients presenting with respiratory symptoms and signs. I would estimate that such biopsies are undertaken in 10 to 15%. Your patient may well have fallen into this group, given that the chest radiographs are somewhat atypical and that at the time of presentation the patient had good arterial blood gases and would have coped well even had he developed a pneumothorax following the investigation.

Clinical diagnoses:

1. *Pneumocystis carinii* pneumonia
2. Adult respiratory distress syndrome

Pathology (*Dr S Lucas*)

The patient was thin but not wasted. There were numerous lesions of Kaposi's sarcoma on the skin, some of which had a white halo indicating regression. Internally, the major findings were in the lungs. Before coming to them, let me summarise the findings in the other viscera. The heart was normal. In the gastrointestinal tract there were lesions of Kaposi's sarcoma on the palate, tongue, oesophagus and small bowel (in this latter site lesions up to 5 mm diameter were seen). The colo-rectum was normal. Microscopy of the intestine did not reveal CMV infection. The liver showed only fatty change. Lymph nodes and spleen were atrophic. The bone marrow was of normal colour and microscopically was cellular, displaying increased haemosiderin (a common finding in patients with AIDS); megakaryocytes were normal in appearance and quantity. In the adrenals there was histological evidence of CMV adrenalitis with some foci of necrosis. The brain weighed 1400 g and was entirely normal, both grossly and histologically.

The larynx, trachea and bronchi were congested and contained no Kaposi's sarcoma, in fact there was no evidence of Kaposi's sarcoma anywhere in the lungs. Both lungs were very heavy, the left lung weighed 1450 g (normal = 560 g), and the right 1700 g (normal = 620 g). A fibrinous exudate was visible on the pleura. On section of the lungs there was complete meaty-red consolidation. Under the microscope this was seen to be the result of two

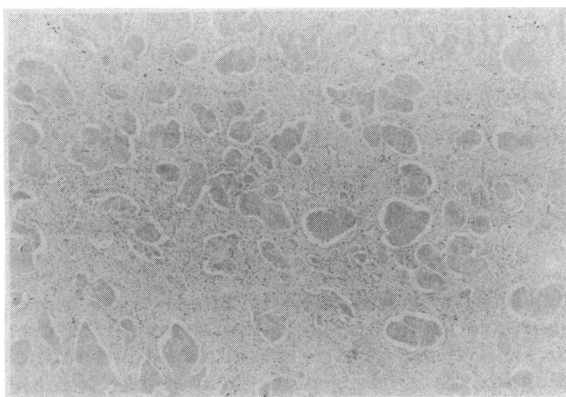


Figure 5 Lung ($\times 10$ magnification). The normal architecture is destroyed. Clusters of *Pneumocystis carinii* (pale amorphous material) lie within the remaining alveoli. Extensive interstitial fibrosis is evident (H and E).

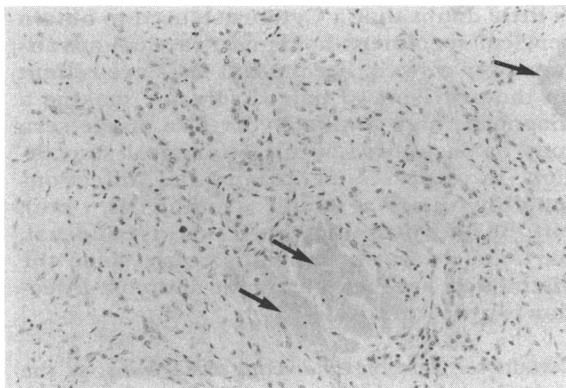


Figure 6 Lung ($\times 200$ magnification). Two residual alveoli both contain *Pneumocystis carinii* (arrows). Proliferating fibroblasts are seen in the interstitium. (H and E).

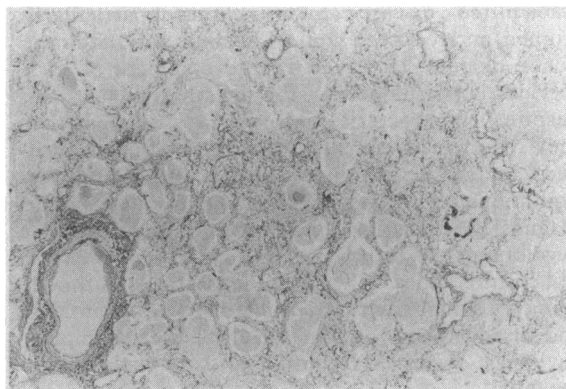


Figure 7 Lung ($\times 10$ magnification). There is a considerable increase of elastic tissue in the interstitium. A small artery is visible in the bottom left corner of the figure. (Elastic Van Gieson).

distinct processes. Firstly *Pneumocystis carinii* pneumonia and secondly pulmonary fibrosis (fig 5); in all zones there were persistent *Pneumocystis carinii* lying within the alveoli. The alveoli were lined with necrotic material and foci of hyaline membrane (adult respiratory distress syndrome) were clearly evident, but the most impressive abnormality was the amount of interstitial fibrosis (fig 6). The alveolar architecture was greatly distorted and active fibroplasia was evident (fig 7). No CMV inclusions nor acid-fast bacilli were seen in the lungs.

The pathogenesis of the adult respiratory distress syndrome must include *Pneumocystis carinii* pneumonia and this contributed to the severe fibrosis. However, even without coexistent adult respiratory distress syndrome *Pneumocystis carinii* pneumonia can result in diffuse pulmonary fibrosis if there is persistent infection of the lung.

Pathological diagnoses

1. *Pneumocystis carinii* pneumonia
2. Adult respiratory distress syndrome
3. Diffuse pulmonary fibrosis
4. Kaposi's sarcoma of skin and gut

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